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REC'D 28 JUN 2000
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I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

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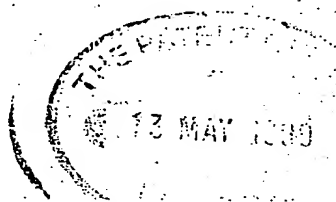
Dated 24 May 2000

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For official use

Your reference

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Notes

Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071-438 4700).

Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.

② Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

Warning

After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977 and will inform the applicant if such prohibition or restriction is necessary. Applicants resident in the United Kingdom are also reminded that under Section 23, applications may not be filed abroad without written permission unless an application has been filed not less than 6 weeks previously in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction revoked.

The
Patent
Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

1 Title of invention

- 1 Please give the title of the invention Treatment of cancers

2 Applicant's details☐ **First or only applicant**

- 2a If you are applying as a corporate body please give:

Corporate name

Pharma Mar, S.A.

Country (and State
of incorporation, if
appropriate)

- 2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

- 2c In all cases, please give the following details:

Address

Calle de la Calera, 3,
Poligono Industrial de Tres Cantos,
28760 Tres Cantos, Madrid, Spain

UK postcode
(if applicable)

Country

ADP number
(if known)

4381161 002

2d, 2e, 2f: If there are further applicants please provide details on a separate sheet of paper.

2d Second applicant (if any)

2d If you are applying as a corporate body please give:

Corporate name

Country (and State
of incorporation, if
appropriate)

2e If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2f In all cases, please give the following details:

Address

UK postcode
(if applicable)

Country

ADP number
(if known)

③ An address for service in the United Kingdom must be supplied

Please mark correct box

③ Address for service details

3a Have you appointed an agent to deal with your application?

Yes ☒

No ☐ → go to 3b

↓
please give details below

Agent's name

Marks & Clerk

Agent's address

57-60 Lincoln's Inn Fields
LONDON
WC2A 3LS.

Postcode

Agent's ADP
number

18001

3b: If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

Address

Postcode

ADP number
(if known)

Daytime telephone
number (if available)

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The answer must be 'No' if:
any applicant is not an inventor
there is an inventor who is not an
applicant, or
any applicant is a corporate body.

8 Please supply duplicates of
claim(s), abstract, description and
drawing(s).

Please mark correct box(es)

9 You or your appointed agent (see
Rule 90 of the Patents Rules 1990)
must sign this request.

Please sign here →

A completed fee sheet should
preferably accompany the fee.

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark correct box

Yes ☐

No ☒

A Statement of Inventorship on Patents
Form 7/77 will need to be filed (see Rule 15).

8 Checklist

8a Please fill in the number of sheets for each of the following types of
document contained in this application.

Continuation sheets for this Patents Form 1/77

Claim(s)

Description

 3

Abstract

Drawing(s)

8b Which of the following documents also accompanies the application?

Priority documents (please state how many)

Translation(s) of Priority documents (please state how many)

Patents Form 7/77 – Statement of Inventorship and Right to Grant
(please state how many)

Patents Form 9/77 – Preliminary Examination/Search

Patents Form 10/77 – Request for Substantive Examination

9 Request

I/We request the grant of a patent on the basis of this application.

Signed

Marks & Clerk

Date

13-5-99

(day month year)

Please return the completed form, attachments and duplicates
where requested, together with the prescribed fee to:

☐ The Comptroller
The Patent Office
Cardiff Road
Newport
Gwent
NP9 1RH

or

☐ The Comptroller
The Patent Office
25 Southampton Buildings
London
WC2A 1AY

Treatment of Cancers

The present invention relates to the treatment of cancers.

US Patent 5,089,273 relates to compounds identified as ecteinascidins. In particular, it relates to ecteinascidins 729, 743, 759A, 759B and 770. The compounds are disclosed to have antibacterial properties and some are also useful as antitumor agents.

We have now found that ecteinascidin 743 has exceptional activity in the treatment of sarcomas and mesotheliomas. A sarcoma is a cancer arising from connective tissue such as muscle or bone. A mesothelioma is a tumour of the mesothelium of the pleura, pericardium or peritoneum.

Thus, the present invention provides a method of treating any mammal, notably a human, affected by a sarcoma or mesothelioma which comprises administering to the affected individual a therapeutically effective amount of ecteinascidin 743, or a pharmaceutical composition thereof. Examples of human sarcomas to be treated include osteosarcomas and soft tissue sarcomas, leiomyosarcomas, fibrosarcomas and mesotheliomas.

The present invention also relates to pharmaceutical preparations, which contain as active ingredient ecteinascidin 743, as well as the processes for its preparation.

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules, etc.) or liquid (solutions, suspensions or emulsions) with suitable composition or oral, topical or parenteral administration, and they may contain the pure compound or in combination with any carrier or other pharmacologically active compounds. These compositions may need to be sterile when administered parenterally.

Administration of the composition of the present invention may be by any suitable method, such as intravenous infusion, oral preparations, intraperitoneal and intravenous administration. Intravenous delivery may be carried out over any suitable time period, such

as 12 to 24 hours or even longer if required, at suitable intervals of say 2 to 4 weeks. Pharmaceutical compositions containing ecteinascidin 743 may be delivered by liposome or nanosphere encapsulation, in sustained release formulations or by other standard delivery means.

The correct dosage of ecteinascidin 743 of this invention will vary according to the particular formulation, the mode of application, and the particular *situs*, host and tumour being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

The compositions of this invention may be used with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or a different time. The identity of the other drug is not particularly limited, and suitable candidates include:

- a) drugs with antimitotic effects, especially those which target cytoskeletal elements, including microtubule modulators such as taxane drugs (such as taxol, paclitaxel, taxotere, docetaxel), podophylotoxins or vinca alkaloids (vincristine, vinblastine);
- b) antimetabolite drugs such as 5-fluorouracil, cytarabine, gemcitabine, purine analogues such as pentostatin, methotrexate);
- c) alkylating agents such as nitrogen mustards (such as cyclophosphamide or ifosfamide);
- d) drugs which target DNA such as the anthracycline drugs adriamycin, doxorubicin, pharmorubicin or epirubicin;
- e) drugs which target topoisomerases such as etoposide;
- f) hormones and hormone agonists or antagonists such as estrogens, antiestrogens (tamoxifen and related compounds) and androgens, flutamide, leuprorelin, goserelin, cyprotrone or octreotide;
- g) drugs which target signal transduction in tumour cells including antibody derivatives such as herceptin;

- h) alkylating drugs such as platinum drugs (cis-platin, carboplatin, oxaliplatin, paraplatin) or nitrosoureas;
- i) drugs potentially affecting metastasis of tumours such as matrix metalloproteinase inhibitors;
- j) gene therapy and antisense agents;
- k) antibody therapeutics; and
- l) other bioactive compounds of marine origin, notably the didemnins such as aplidine.

The present invention also extends to the compounds for use in a method of treatment, and to the use of the compounds in the preparation of a composition for treatment of cancer.

Example

Eleven patients (9 soft tissue sarcomas and 2 osteosarcomas) received ET-743, 10 at a dose of $1500 \mu\text{g}/\text{m}^2$ and one at the maximum tolerated dose of $1800 \mu\text{g}/\text{m}^2$. Nine were treated in a phase I clinical trial, while two received ET-743 on a compassionate use basis. Sex 6 men/5 women; median age 37 years (16 to 71); median number of previous chemotherapy regimes 2 (1 to 4), all patients pretreated with anthracyclines and alkylators; median PS 1 (0 to 2); median number of metastatic sites 2 (1 to 3).

Et-743 was administered by 24 hours continuous infusion every three weeks, over 38 cycles.

Two partial responses were obtained, one lasting over four months, two minor responses, and three stabilisations lasting over four months. Among the two osteosarcomas, there was one partial response and one minor response, both still ongoing (WHO criteria).

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